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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Eva KONTSEKOVA
Peter FILIPCIK

Serial No.: 10/521,049

Filed: November 1, 2005

For: TRANSGENIC ANIMAL EXPRESSING ALZHEIMER'S TAU PROTEIN

Confirmation No.: 5434

Group Art Unit: 1633

Examiner: Leavitt, Maria Gomez

Atty. Dkt. No.: SONN:066US

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September 21, 2009
Date

Travis M. Wohlers

REPLY BRIEF

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 23313-1450

Commissioner:

Appellant submits this Reply Brief to the Board of Patent Appeals and Interferences in response to the Examiner's Answer mailed July 20, 2009 ("Examiner's Answer"). A Request for Oral Hearing is being filed herewith. The required fees in the amount of $540.00 in connection with the filing of the Request for Oral Hearing are being charged to a credit card through EFS-Web concurrently with this submission. The Commissioner is hereby authorized to deduct any underpayment of fees or charge any additional fees required under 37 C.F.R. §§ 1.16 to 1.21 in connection with the filing of this paper from the Fulbright & Jaworski Deposit Account No. 50-1212/SONN:066US

I. APPELLANT'S REPLY TO THE ARGUMENTS MADE IN THE EXAMINER'S ANSWER

The enablement rejection is maintained in the Examiner's Answer. Appellant disagrees with this rejection and incorporates by reference the arguments set forth in the Appeal Brief. Appellant submits the following additional comments in reply to the Examiner's Answer.

A. The Specification Provides an Enabling Disclosure of How to Make and Use a Transgenic Non-Human Animal

1. A Correlation Between the Phenotype and the Tauopathy has Been Established

The Examiner asserts that "Appellant fails to provide any useful correlation of the claimed phenotypes associated with Alzheimer's disease . . . such that one of skilled [sic] in the art could make and use a transgenic non-human animals in any of the contemplated treatment, prevention and/or diagnosis of a tauopathy in a useful way." Examiner's Answer, p. 16. As explained in the Appeal Brief, the transgenic animals encompassed by the current claims are useful models of diseases exhibiting neurofibrillary pathology, including Alzheimer's disease. In particular, the transgenic animals encompassed by the current claims exhibit not only the most important and earliest immunohistochemical finding in Alzheimer's disease (*i.e.,* neurofibrillary pathology), but also exhibit other pathological features that are associated with Alzheimer's disease including cognitive impairment, oxidative stress, hypertension, and diabetes. *See* First Filipcik Declaration, para. 11; Cente *et al.* (Eur J Neurosci., 24(4):1085-90 (2006).

2. A Reproducible Phenotype Can be Achieved from Different Animal Strains and Different Insertional Events

The Examiner acknowledges that the record "indisputably disclose[s] the creation of three independent transgenic founder lines, e.g., #318, #72, and #24 that stably expressed human

truncated tau displaying similar phenotype." Examiner's Answer, p. 17. As explained in the Appeal Brief, the phenotype produced by transgenic truncated tau expression was not dependent on genetic background, as the transgene was transferred from the genetic background of the hypertensive SHR strain into the normotensive Wistar strain. In this new genetic environment, an almost identical phenotype at the level of biochemical examination and behavioral measurements was observed. Thus, it is clear that a reproducible phenotype can be achieved from different genetic backgrounds.

The Examiner further asserts that "there is not sufficient evidence for any transgenic non-human animal having germ and/or somatic cells with a reproducible phenotype that can be achieved from different insertional events." Examiner's Answer, p. 17. As explained in the Appeal Brief, in addition to transgenic rat line #318, transgenic rat lines #24, #72 (SHR and WKY genetic backgrounds), and SHR24/72 were also created. Transgenic rat line #24 contains a cDNA coding for human tau protein that is shorter by 93 nucleotides (31 amino acids) than the cDNA coding for human tau protein in transgenic rat line #318. The same construct as used in the generation of transgenic rat line #318 also was used in the generation of transgenic rat line #72. The onset and progression of neurodegeneration is the same in all three transgenic rat lines (*i.e.* Tg lines #24, #72, and #318). The only observed difference has been that the life span of those animals containing 4 repeat tau (*e.g.* Tg line #72) is much shorter when compared to those animals containing 3 repeat tau region (*e.g.* Tg line #24) of human tau protein. *See* Second and Third Filipcik Declarations. Thus, in addition to demonstrating that a reproducible phenotype can be achieved from different animal strains, transgenic rat lines #318, #72 and #24 also

demonstrate show that a reproducible phenotype can be achieved from different insertional events.

3. Non-Human Transgenic Animals are Enabled

The Examiner also asserts that there is no evidence "for enablement of non-human transgenic animals having germ and/or somatic cells[,] such animals exhibiting characteristics that make them suitable models for Alzheimer's disease, let alone any tauopathy." Examiner's Answer, p. 19. It was previously demonstrated that in rats, a construct encompassed by the claims resulted in Alzheimer's disease-associated neurofibrillary pathology. As explained in detail in the Appeal Brief, a person of skill in the art would recognize that a variety of animal models would be suitable Alzheimer's disease (AD) models, as AD associated neurofibrillary pathology, based on paired helical filaments, occurs in a number of animals. Therefore, it was known that tau could be expressed in several distinct animal species.

The Examiner acknowledges that "Lewis *et al.*, (2000) clearly teaches the pleitropic role of neurofibrillary tangles in mice expressing the human tau containing the most common FTDP-17 mutation (P201L)." Examiner's Answer, p. 18. The Appeal Brief further explains that in addition to ***rats*** and ***mice***, Hartig *et al.* (European Journal of Neuroscience, Vol. 25, pp. 69–80, 2007) shows that PHF-like tau occurs in ***hamsters***, which parallels the situation in AD. Hartig also notes that PHF-like tau was observed in ***ground squirrels*** (p. 69, right col., para. 2). Huang *et al.*, (Brain Research 771, 1997, 213–220) describes neurofibrillary tangles based on abnormal tau in ***rabbits***. Gotz (Brain Research Reviews 35 (2001) 266–286) is a review article that describes several transgenic animal models, including the use of murine models expressing tau as system for the dysfunction of tau and neurodegeneration and dementia based on neurofibrillary

lesions (abstract, p. 275, right col., item 4.3). These references demonstrate that a variety of animals are capable of exhibiting NF pathology and, therefore, are suitable for the study of NF pathology and Alzheimer's disease. Moreover, the specification, the Lewis publication, and the Gotz publication demonstrate that a tau transgene can be successfully expressed in rat, mouse, and lamprey. In view of the above, the claims are enabled for any non-human transgenic animals and the evidence demonstrates that such animals exhibit characteristics that make them suitable models for Alzheimer's disease.

4. The Cited References Support the Enablement of the Current Claims

The Examiner cites a variety of references that discuss individual differences between species leading to different expressions and unpredictable results in an attempt to demonstrate the unpredictability of the potential variability in transgenic animals. Examiner's Answer, p. 6-10. However, these cited publications do not relate to or discuss the expression of tau protein as described in the present invention and cannot support the enablement rejection.

With respect to the Lewis reference, the Examiner asserts that "the mere recitation that it is 'conventional practice' for the skilled artisan to deal with the variability of a method to generate transgenic animals does not render the instant invention enabled, as the skilled artisan will have to engage in undue experimentation to determine unknown predictability." Examiner's Answer, p. 20. As explained in the Appeal Brief, potential limitations of transgenic animal experiments were well known to those in the art. Further, dealing with such limitations was a conventional practice, as those having skill in the art are aware of the manner in which these limitations may be overcome. For example, Williams states that "[i]t is mandatory for most purposed to assess at least two independent lines." Williams, p. 1124, col. 2, 3rd paragraph; *see*

also Sigmund, p. 1428, col. 1, 3rd paragraph (it is "the responsibility of the investigator to use common sense and design the best possible control experiments that fit the individual situation, to assess whether the phenotype observed in their model is due specifically to the targeted modification or is affected by other loci."). Thus, a person having skill in the art would not have to exercise undue experimentation in order to overcome these potential limitations. *See In re Angstadt*, 537 F.2d 498, 503 (CCPA 1976) ("we believe that the experimentation required . . . would not be undue and certainly would not 'require ingenuity beyond that to be expected of one of ordinary skill in the art.'" (quoting *Fields v. Conover*, 58 CCPA 1366, 1372, 443 F.2d 1386, 1390-91 (1971))). Here, the performance of trial runs "is 'reasonable,' even if the result of each trial is uncertain." *See In re Colianni*, 561 F.2d 220, 224 (CCPA 1977) (Miller, J. concurring).

The Examiner asserts that "the Moreadith reference not only refers to the unpredictability of generating transgenic hamster, pig, sheep, cattle, rabbit, rat, mink, and monkey by using ES cells but also to the unpredictability of transgenics generated by introducing foreign genes by microinjection into fertilized eggs." Examiner's Answer, p. 21. As explained in the Appeal Brief, Moreadith (1997) does not teach that stem cell technology and methods employed to create knock-out mice is limited to mice, but merely states that this particular technology had not yet been applied to hamster, pig, sheep, cattle, rabbit, rat, mink, monkey, and humans (Summary, p. 214). Moreadith noted that it ***seemed likely*** that the technology would be advanced into these additional species over the next few years (Summary, p. 14). Further, the Moreadith reference is discussing a particular stem cell technology, but the presently claimed invention is not limited to the use of stem cells. Accordingly, any argumentation that ES cells from different organisms may have different features and might in certain cases not continue developing during

embryogenesis does not mean that one could not make and use the claimed invention because the claimed invention is not limited to transgenic animals created from ES cells. An applicant need only provide an enabling disclosure for ***the claimed invention***. *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991). Finally, Moreadith specifically states that "[t]he development of transgenic technology, whereby genes (or mutations) can be stably introduced into the germline of experimental mammals, ***allows investigators to create mice of virtually any genotype*** and to assess the consequences of these mutations in the context of a developing and intact mammal." (Moreadith (1997), Abstract) (emphasis added).

Finally, the Examiner asserts that "post filing art by Keefer *et al.*, brings similar insight into the lack of predictability of generating any transgenic animal as the author recognizes the inefficiency of pronuclear microinjection in transgenic techniques." Examiner's Answer, p. 21. As explained in the Appeal Brief, Keefer actually discusses the ***inefficiency*** of pronuclear microinjection in generating transgenic animals. Inefficiency and unpredictability are not equivalent, as something can be inefficient ***and*** predictable. In fact, it is clear that while pronuclear transfer in cattle, sheep, and goats may be inefficient, the state of pronuclear injection as described in Keefer is such that it is routine and reasonable to inject a few hundred to a thousand oocytes, depending on the animal, to produce a founder transgenic animal. Keefer does not appear to show any concern as to whether the transgenic animal will express the desired protein, only a concern as to whether the animal will express high amounts of the protein (Keefer, p. 6-7).

B. A Person Having Skill in the Art Would be Able to Make and Use a Variety of Promoters with the Current Claims

The Examiner asserts that "[d]ue to the lack of the direction for sequences responsible for brain-specific regulation of a truncated tau gene resulting in the claimed transgenic phenotype, the claimed invention would have required one skilled in the art to engage in an undue amount of experimentation without a predictable degree of success to achieve the specific claimed phenotype for any non-human transgenic animal." Examiner's Answer, p. 24. As explained in the Appeal Brief, a person of ordinary skill in the art would have had a number of known, suitable promoters at his disposal at the time the application was filed. A person of ordinary skill in the art would further understand that the promoter in the DNA construct is a promoter suitable for expression in mammalian cells, and methods for the preparation and evaluation of useful DNA constructs is taught in the specification. Specification, p. 12, ln. 12-38. Thus, someone of ordinary skill in the art would have had a number of known, suitable promoters at his disposal at the time the application was filed.

As also explained in the Appeal Brief, it would require only routine cloning procedures, such as those described in the present specification or in Sambrook *et al.*, to place a cDNA molecule coding for N- and C-terminally truncated tau molecules under the control of an appropriate promoter. The Examiner acknowledges that "the manipulation of previously identified DNA fragments and cell transformation systems is within the ordinary level of skill in the art of molecular biology." Examiner's Answer, p. 24. In light of the availability of known promoters and the level of ordinary skill in the art, the nature of experimentation required to practice the full scope of the claim would not be undue. *See Angstadt*, 537 F.2d at 503. It is the nature of the experimentation required to enable the full scope of a claim, not the quantity of

experimentation, which is important. *Colianni*, 561 F.2d at 224. Accordingly, the specification provides an enabling disclosure of promoters for the current claims.

C. Claims 19 and 37 Are Separately Patentable

In addition to the arguments presented above, Appellants separately argue the patentability of claims 19 and 37. Claims 19 and 37 are both directed to a transgenic rat. The Examiner acknowledges that the specification is enabling for a transgenic rat. Examiner's Answer, p. 4. The Examiner also acknowledges that "independent claims 17 and 37 only require the production of neurofibrillary (NF) pathology producing activity when the truncated human tau product is expressed in the brain cells of rats." Examiner's Answer, p. 24. However, the Examiner expresses concerns about germline transmission and the number of cells in the rat that contain the transgene. Examiner's Answer, p. 24. As explained in the Appeal Brief, these concerns are misplaced because claims 19 and 37 do not include or require germline transmission or a number of cells containing the construct. *See e.g., Ex parte Chen*, 61 U.S.P.Q.2D (BNA) 1025, 1028 (BPAI 2001) (non-precedential). The only other basis that the Examiner has presented for rejecting claims 19 and 37 is for lack of enablement of promoters that could drive the expression of the cDNA molecule comprising SEQ ID NO: 9. However, claims 19 and 37 do not contain a limitation on the amount of transgene expression. Moreover, for the reasons discussed above and in the Appeal Brief, the specification provides an enabling disclosure of suitable promoters that could drive the expression of the cDNA molecule recited in the claims.

D. Claim 34 Is Separately Patentable

In addition to the arguments presented above, Appellants separately argue the patentability of claim 34. The Examiner acknowledges that "[b]ecause the specification successfully teaches the generation of transgenic rodents and transgenic mice expressing the

P301L mutant tau, which phenotype mimics features of human tauopathies, it would require undue experimentation for one of ordinary skill in the art to make and use the transgenic non-human mouse." Examiner's Answer, p. 25. It is unclear how it would require undue experimentation to make and use the transgenic non-human mouse when it is acknowledged that the specification successfully teaches the generation of transgenic mice. Regardless, as explained in the Appeal Brief, the specification teaches that one could also make and use a transgenic mouse encompassed by the current claims. Thus, the fact that (1) the methods in the specification successfully produced a transgenic rodent encompassed by the claims, and (2) transgenic mice expressing P301L mutant tau, which were shown to mimic features of human tauopathies, had been created (*see e.g.,* Lewis *et al.*) establish that it would not have required undue experimentation to make and use a transgenic mouse as recited in claim 34.

II. CONCLUSION

For at least the reasons stated above (and those in the Appeal Brief), Appellant requests that the Board overturn the rejections of claims 17-37.

Respectfully submitted,

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